ADVISORY COMMITTEE BRIEFING MATERIALS: AVAILABLE FOR PUBLIC RELEASE

PERIPHERAL AND CENTRAL NERVOUS SYSTEM DRUGS

ADVISORY COMMITTEE

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ADDENDUM TO

DRISAPERSEN BRIEFING DOCUMENT

NDA 206031

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INTRODUCTION:

This addendum to BioMarin's Advisory Committee Briefing document includes data that was submitted to the Division of Neurology Products in response to discussions and agreements made between BioMarin and the Agency during the Late Cycle Meeting (LCM) of 05 November 2015, wherein it was agreed that BioMarin would submit additional analyses of the three completed randomized placebo-controlled studies, 117 (Study 1), 876 (Study 2), and 044 (Study 3) to demonstrate consistent evidence of effectiveness for drisapersen (TOPIC 1). This addendum also includes results from an analysis to address potential expectation bias due to injection site reactions for all three placebo-controlled studies (TOPIC 2).

TOPIC 1: CONSISTENT EVIDENCE OF EFFECTIVENESS - POOLED ANALYSIS

The primary aim of these analyses is in response to Agency feedback provided during the drisapersen Late Cycle Meeting (05 November 2015) for the need to demonstrate consistent evidence of effectiveness of drisapersen on 6MWD. Specifically:

- While Studies 117 and 876 demonstrated robust evidence of treatment benefit on the 6 minute walk distance (6MWD) at Week 24 (35m, p=0.01, and 27m, p=0.07, respectively), these findings were not substantiated by the intent to treat (ITT) analysis from the largest study in the program, Study 044.
- Study 044 enrolled patients over a wider range of baseline eligibility because there was no limit on baseline rise from floor, unlike Studies 117 and 876 in which baseline rise from floor (RFF) was restricted to less than 7 seconds. In this study 044, a smaller magnitude of improvement in 6MWD was observed (10m at Week 48, p=0.4).
- Moreover, an "obvious" first level subgroup analysis in patients from Study 044 whose RFF was less than 7 seconds (similar to the eligibility criteria of Studies 117 and 876) demonstrated a benefit of improvement in 6MWD to a lesser degree (5m) compared to that observed in the contemporaneously conducted Studies 117 and 876. The sponsor's view is that the patients whose rise from floor was <7 seconds in Study 044 were not in fact sufficiently comparable to those patients in Studies 117 and 876 to draw a proper comparison.
- It is acknowledged that Study 044 enrolled patients who were older and had worse baseline 6MWD. BioMarin previously used literature-based "cut-points" for the prognostic factors of baseline walk and age to explore efficacy in patients more similar to those enrolled in Studies 117 and 876. However, these analyses were sensitive to where the cut points were made, both in terms of parameter estimates and nominal levels of significance.

At the LCM, BioMarin presented an updated analysis of Study 044 intended to demonstrate substantiation of the findings of Studies 117 and 876. The present

submission provides documentation and analysis of the concepts discussed at this meeting, and offers interpretation of the findings.

The approach taken was to examine the pooled study population, randomized to either placebo (n=95) or 6 mg/kg/week (n=161) across the 3 placebo-controlled studies, and to identify a group of patients whose baseline characteristics were comparable among all three studies with respect to two key baseline predictive factors: 6MWD and RFF. The intent of this effort was to evaluate whether results in comparable populations of Study 044 and Studies 117 and 876 were consistent with one another.

To enable comparison across studies, a comparable group of patients enrolled across the 3 studies was identified based on quintiles of baseline RFF and baseline 6MWD across the pooled population as shown in Appendix A. The entire range of baseline characteristics for both RFF (min, max = 0.5s to "unable to perform") and 6MWD (min, max = 107 to 566m) was examined, and the middle 50% of subjects from these analyses of the pooled population were selected for analysis. This approach removes the 25% most severely affected and the 25% least severely affected subjects from the analysis, and includes a sufficient sample size between treatment groups to enable interpretable results.

Based on this selection criterion, subjects had either a baseline 6MWD between 313 to 419m or a baseline RFF between 4.2 and 13.3 seconds. Using these two groupings of subjects, the treatment effect was analyzed in the pooled study population, and by each study individually. These analyses show that improvement in 6MWD observed in the pooled population is similar (in both direction and approximate magnitude) as in Study 044. This result is true for populations defined by either baseline RFF (Table 1) or baseline 6MWD (Table 2). Parameter estimates, 95% confidence intervals, and nominal p-values are provided for descriptive purposes.

Table 1. Treatment Effect at Week 48 in 6MWD By Study and Pooled in Subjects from Studies 117, 876, and 044 with Baseline RFF between 4.2s and 13.3s

	Study				
	Pooled 044/117/876 (N=79/46)	044 (N=58/28)	Pooled 117/876 (N=21/18)	117 (N=10/12)	876 (N=11/6)
Mean difference (meters) drisapersen vs. Placebo	25.8	18.1	36.6	31.4	35.6
95% CI	(5.1, 46.6)	(-9.2, 45.6)	(4.2, 69.0)	(-22.3, 85.1)	(-3.1, 74.3)
P value	0.015	0.191	0.028	0.236	0.069

Note: For pooled analysis, model includes study ID, treatment, visit, treatment by visit, baseline 6MWD, baseline 6MWD by visit. For analysis within each study, model includes treatment, visit, treatment by visit, baseline 6MWD, baseline 6MWD by visit. N's are presented as 6 mg/kg drisapersen/placebo.

Table 2. Treatment Effect at Week 48 in 6MWD By Study and Pooled in Subjects from Studies 117, 876, and 044 with Baseline 6MWD between 313m and 419m

	Study				
	Pooled 044/117/876 (N=76/52)	**044 (N=56/32)**	**Pooled 117/876 (N=20/20)**	**117 (N=8/13)**	**876 (N=12/7)**
Mean difference (meters) drisapersen vs. Placebo	31.3	19.9	55.6	72.8	37.1
95% CI	(9.3, 53.2)	(-8.8, 48.7)	(19.8, 91.3)	(12.4, 133.1)	(-5.0, 79.2)
P value	0.006	0.171	0.003	0.021	0.080

Note: For pooled analysis, model includes study id, treatment, visit, treatment by visit, baseline 6MWD, baseline 6MWD by visit. For analysis within each study, model includes treatment, visit, treatment by visit, baseline 6MWD, baseline 6MWD by visit. N's are presented as 6 mg/kg drisapersen/placebo.

Note is taken that the parameter estimates and nominal p-values of the populations defined by these baseline characteristics do not produce identical results among the studies. A plausible explanation is that rise from floor and 6MWD do not exactly overlap in the same patients.

Some interpretive caveats warrant explicit mention in the context of these analyses. First, this effort is not intended to suggest that a post-hoc analysis of a subgroup of Study 044 provides "stand alone" statistically robust evidence of treatment benefit. Rather, the intention is to demonstrate that the strong findings of Studies 117 and 876 are in fact substantiated by relatively similar findings in Study 044 in the population of Study 044 whose baseline predictive characteristics are similar to those represented in Studies 117 and 876. Second, identifying this more responsive population does not necessarily imply that there is no benefit in the remaining population. The aim is to demonstrate that study 044 does not negate the findings of studies 117 and 876.

Taken together, we believe that these data substantiate the strong efficacy findings of Studies 117 and 876, and provide substantial evidence of efficacy.

TOPIC 2: ANALYSIS TO ADDRESS POTENTIAL EXPECTATION BIAS DUE TO ISRS

The Agency raised concern in the FDA Advisory Committee briefing document that treatment allocation may have been substantially unmasked in the clinical trials because of a high incidence of injection site reactions (ISRs) from drisapersen, and that 6MWD results may have been affected by patient and investigator expectation bias if treatment assignments could be deduced. Importantly, the magnitude and

nature of ISRs over 48 weeks in placebo-treated and drisapersen-treated patients was not known at the time all three randomized trials began because the only data available at the start of those studies was obtained from uncontrolled, shorter-term studies. So there was an expectation of equipoise at the start of the studies. Additionally, the studies were designed such that those who assessed 6MWD were separate from those who might have knowledge of the administration of study medication or clinical evaluation of the patient. In addition, it is important to remember that the 3 studies were conducted contemporaneously.

In order to assure that 6MWD was in fact not biased by ISRs, further analysis of the collected data was undertaken. 6MWD results were compared between subjects with and without ISRs who were treated with drisapersen 6 mg/kg/week, to determine whether the presence or absence of ISRs influenced treatment outcomes (Table 3). In general terms, change from baseline 6MWD was worse, or comparable, in patients who experience ISRs compared to patients who do not experience ISRs. These analyses corroborate the unbiased nature of efficacy assessments, and provide evidence that suspected expectation bias affecting 6MWD results was unlikely.

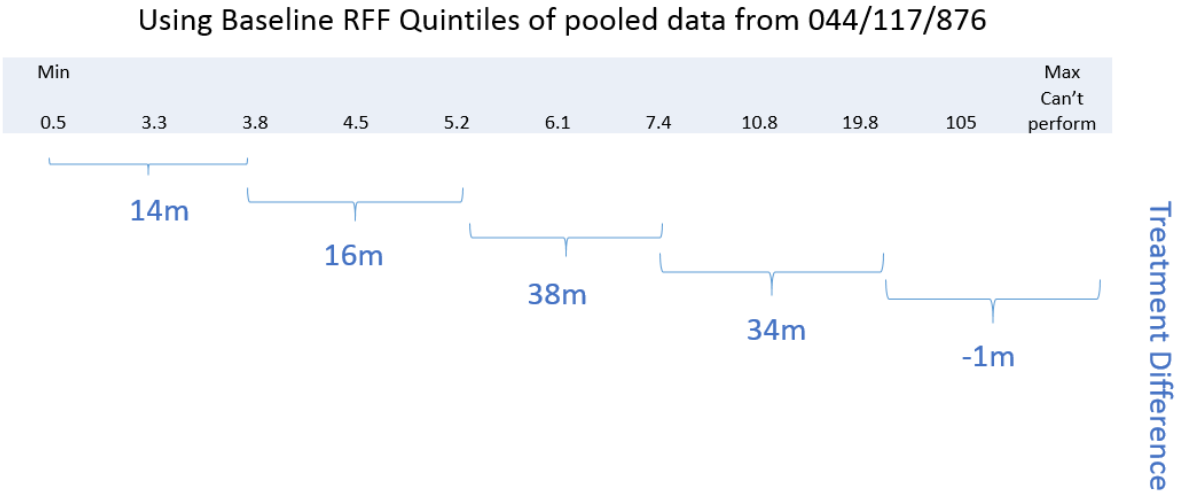
Table 3: Adjusted Mean Change from Baseline at Week 48 in 6MWD in Subjects Treated with Drisapersen 6 mg/kg/week, With and Without ISRs

Study	Any ISR (Y/N)	N	Adj Mean Change from Baseline in 6MWD (m)	SE
Study 044	Y	89	-51	9
	N	28	-24	16
Study 117	Y	14	8	20
	N	4	4	22
Study 876	Y	13	6	13
	N	5	35	16

Note: For analysis within each study, MMRM model includes treatment, visit, treatment by visit, country grouping, baseline 6MWD, baseline 6MWD by visit.

APPENDIX A: Treatment Estimates (Change from Baseline at Week 48 in 6MWD: Difference in Unadjusted Means between Treatment and Placebo) using Baseline Quintiles of Pooled Data from Studies 044, 117, and 876.

Baseline RFF Analysis:



Baseline 6MWD Analysis: